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EFFECTS OF SOME ANTIMOTION SICKNESS DRUGS AND SECOBARBITAL ON POSTURAL EQUILIBRIUM FUNCTIONS AT SEA LEVEL AND AT 12,000 FEET (SIMULATED)

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This study was undertaken to determine the effects of six antimotion sickness drugs, three placebos, and secobarbital on postural equilibrium functions at sea level and at 12,000 feet (chamber simulated) These effects, as defined by performance on a quantitative ataxia test battery, were investigated on nine normal men.

Analysis of variance revealed that, relative to the other drugs and placebos, only secobarbital had a deleterious effect on the performance skills studied--both at sea level and at 12,000 feet--whereas none of the antimotion sickness drugs alone or in combination differed significantly from placebos in having such an effect in either environment. This finding was highly consistent and in keeping with the known depressant effects of secobarbital on CNS activity.

Among the antimotion sickness drugs, only the combination of d-amphetamine (10 mg) plus scopolamine (0.6 mg) at altitude had a significant enhancing effect on performance relative to the reverse (depressing) effect found at sea level.

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SUMMARY PAGE

THE PROBLEM

To determine the effects of six antimotion sickness drugs, three placebos, and secobarbital on postural equilibrium functions at sea level and at 12,000 feet (chamber simulated). These effects, as defined by performance on a quantitative ataxia test battery, were investigated on nine normal men.

FINDINGS

Analysis of variance revealed that, relative to the other drugs and placebos, only secobarbital had a deleterious effect on the performance skills studied--both at sea level and at 12,000 feet--whereas none of the antimotion sickness drugs alone or in combination differed significantly from placebos in having such an effect in either environment. This finding was highly consistent and in keeping with the known depressant effects of secobarbital on CNS activity.

Among the antimotion sickness drugs, only the combination of d-amphetamine (10 mg) plus scopolamine (0.6 mg) at altitude had a significant enhancing effect on performance relative to the reverse (depressing) effect found at sea level.

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INTRODUCTION

This study was undertaken to determine if any significant influences on postural equilibrium functions underlying performance on an ataxia test battery would be produced by a single dose of a barbiturate (secobarbital) and of each of several anti motion sickness drugs such as would be taken alone or in combination to prevent acute motion sickness (24). Although motion sickness certainly may disrupt performance, there is resistance to using antimotion sickness drugs based on a fear of their side effects.

Secobarbital was included in this investigation to determine if its known depressant effects on the central nervous system would show significant effect on postural equilibrium functions. Dependent upon the results, recommendations regarding the use of secobarbital in relation to motion sickness might be possible.

The battery of ataxia (postural equilibrium) tests was selected to monitor performance at sea level and at 12,000 feet altitude simulated in an altitude chamber. We selected 12,000 feet because this represents the maximum altitude at which unpressurized aircraft can be flown safely (3,18); therefore, any effects of altitude added to that of a drug would be most pronounced under such conditions.

PROCEDURE

SUBJECTS

The subjects were nine healthy Navy enlisted men, 18 to 24 years of age (Mean: 19.7 years) and with a body weight of between 125 and 215 pounds (Mean: 155.3 pounds), assigned to this laboratory as volunteer research subjects and selected on the basis of a comprehensive medical (including audiological and vestibular) evaluation. All were susceptible to motion sickness as determined by the dial test on the Pensacola slow rotation room (14).

METHOD

Seven drugs were pulverized and each was placed in identical gelatin capsules, as were three individual lactose placebos. The drugs tested, their dosage, and the drug numerical code are shown in Table I. Each "drug" was presented once to each subject in each environment according to the double blind order-confounding, Latin-square schedule*, shown in Table II. All subjects were given the same dose of each drug. The numerical coding and, hence, the presentation order for each subject in both environments were identical.

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*The schedule was originally designed for a 10-subject experiment (2); although appropriately applied in the present study, its use with only nine subjects makes it something less than Latin-square.

Table I

Drugs and Dosages Used at Sea Level and at 12,000 Feet Altitude (Simulated)

Generic Name	Symbol	Dose	Drug Numerical Code
scopolamine plus ephedrine	S-E	0.6 mg plus 50 mg	1
placebo 1	PL1	250 mg	2
dimenhydrinate	DRA	50 mg	3
placebo 2	PL2	250 mg	4
placebo 3	PL3	250 mg	5
scopolamine	SCO	0.6 mg	6
secobarbital	SEC	100 mg	7
d-amphetamine	AMP	10 mg	8
d-amphetamine plus scopolamine	A-S	10 mg plus 0.6 mg	9
cyclizine	CYC	50 mg	10

Table II

Latin-Square Used to Schedule the Order of Drug Presentation at Sea Level and at Altitude

Subject Number	Drug Presentation Order (Days)*									
1	1	2	3	4	5	6	7	8	9	10
2	2	4	6	8	10	1	3	5	7	9
3	3	6	9	1	4	7	10	2	5	8
4	4	8	1	5	9	2	6	10	3	7
5	5	10		9	3	8	2	7	1	6
6	6	1	7	2	8	3	9	4	10	5
7	7	3	10	6	2	9	5	1	8	4
8	8	5	2	10	7	4	1	9	6	3
9	9	7	5	3	1	10	8	6	4	2

*Numbers inside the square refer to the drugs as numbered in Table I; the first column represents Day 1, and the second column Day 2, etc.

Tests

The tests were administered about 1 hour after drug intake. The quantitative ataxia test battery has been described in detail previously (9,11). All tests were undertaken while subjects wore hard-soled shoes and were in the stringent position of arms folded against chest, feet aligned heel-to-toe (tandemly), with the exception of the Stand One Leg Eyes Closed tests, and body erect or nearly erect. They were administered in the following order:

1. Sharpened Romberg (SR): standing on the floor with eyes closed for 60 seconds. Maximum score obtainable: 240 seconds.

2. Walk Eyes Open (Walk E/O): walking 5 steps per trial on a 3/4-inch-wide by 8-foot-long rail. Maximum score obtainable: 15 steps.

3. Stand Eyes Open (Stand E/O): standing on the 3/4-inch-wide rail for a maximum of 60 seconds per trial. Maximum score obtainable: 180 seconds.

4. Stand Eyes Closed (Stand E/C): standing on a 2-1/4-inch-wide by 30-inch-long rail for a maximum of 60 seconds per trial. Maximum score obtainable: 180 seconds.

5. and 6. Stand One Leg Eyes Closed (SOLEC-R and SOLEC-L): standing stationary on the floor on each leg for a maximum of 30 seconds on any trial. Maximum score obtainable: 150 seconds on each leg.

7. Walk A Line Eyes Closed (WALEC)[+]: walking a distance of 12 feet on a line on the floor. Maximum score obtainable: 0 inches (of deviation from the line).

At altitude only three of these tests were administered; the sequence of testing was 1) SR, 2) Stand E/O, and 3) Stand E/C.

In the interest of minimizing learning effects under drug conditions, during several days prior to the experiment each subject was retested as often as necessary for maximizing, or plateauing of, performance scores on the ataxia battery.

Under drug conditions all subjects were tested once each weekday (Monday through Friday) during four consecutive weeks; during the first 2-week period testing was at the sea level environment. The 12,000-feet altitude was simulated in the altitude chamber at the Naval Aerospace Medical Institue, where the tests were administered during the second 2-week period.

[+]This subtest of the battery has now been replaced by the WOFEC subtest (10).

RESULTS

To test the effects of sea level versus altitude and the ten drug categories (three placebos and seven drugs) three analyses of variance took the form of 9X2X10 fixed design with repeated measures of nine subjects on the last two factors. The criterion measures were the scores obtained on the three ataxia tests administered under sea-level and simulated altitude conditions: SR, Stand E/O, and Stand E/C. Ten additional analyses of variance were completed on the same subject data to test the simple effects of the drugs at sea level and at altitude (12,000 feet-simulated): three at each level on the three ataxia tests just mentioned and four at sea level only on the other ataxia tests (Walk E/O, SOLEC-R, SOLEC-L, and WALEC).

A summary of the results of the first-mentioned three analyses of variance is given in Table III. The main effect of sea level versus altitude (B) was found to be significant ($p < .01$) only in the Stand E/O test. The main effect of drugs (C) was found to be significant in all three ataxia tests. The interaction effect of sea level versus altitude by drugs (BC) was found to be of marginal significance in the three tests.

As may be noted in part (b), Stand E/O, of Figure 1, which displays the Table III results, the significant sea level versus altitude effect indicates that performance on this test was better at altitude (dashed line above solid line) than at sea level across the ten drugs. The significant effect of drugs within all three ataxia tests indicates that performance under at least one of the drugs differed significantly from another drug condition. As may be noted in the figure, secobarbital (SEC) tended to have the most deleterious effect among the drugs both at sea and altitude levels. (A more definitive analysis of differences between drugs was made in the second set of ten analyses of variance at sea level and at altitude.) It should also be noted that performance at altitude on all three ataxia tests was best under the drug d-amphetamine (AMP) and under the combination d-amphetamine plus scopolamine (A-S), reaching in three cases the ceiling on the tests (perfect score by all nine subjects--denoted by circles). The moderately significant BC interactions are indicated in the figure by the degree of non-parallel profiles (dashed line c.f. solid line). Within (a), SR, the two profiles differ most relative to the combination of drugs scopolamine plus ephedrine (S-E), and to scopolamine (SCO) alone. The profiles in this case cross; performance within the altitude environment under S-E dropped considerably below the mean placebo at sea level and then returned to the ceiling under SCO; while within the sea level environment the converse was evident. Within part (b), Stand E/O, the profiles do not cross, but the difference between altitude and sea level under the combination of drugs d-amphetamine plus scopolamine (A-S) was significantly greater ($p < .01$)* than under any of the other drugs.

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*By using the studentized range statistic and a method developed by Tukey, referred to as a "honestly significant difference" (hsd) (23), comparisons may be made between all possible pairs of the 16 means represented in each part of Figure 1 with the critical hsd differences, 5.1(.05) and 5.8(.01)--SE units of the vertical axis. Analogous critical hsd differences relative to Figures 2 and 3 are: 4.4(.05) and 5.3(.01).

Table III

Summary Analyses of Variance--Sea Level Versus Altitude

Source	df	SR MS	SR F	SR p<	Stand E/O MS	Stand E/O F	Stand E/O p<	Stand E/C MS	Stand E/C F	Stand E/C p<
A (Subjects)	8	6007.44			9969.12			18973.89		
Within Subjects										
B (Sea level versus altitude)	1	154.94	--	ns	67009.61	12.30	.01	29.61	--	ns
B x Subj	8	164.35			5449.37			1081.14		
C (Drugs)	9	5892.15	4.31	.0005	4969.43	2.81	.01	3986.53	4.26	.0005
C x Subj	72	1365.81			1766.90			936.52		
BC	9	1084.09	1.88	.10	2124.52	1.49	.25	916.24	1.33	.25
BC x Subj	72	577.70			1428.43*			688.07*		
SE ($\sqrt{MSe^*/9}$)**		(8.0119)			(12.5982)			(8.7436)		

*Mean Square (MSe) error terms of the interaction of BC x Subj

** Standard error of the means of the Studentized range statistic used in constructing Figure 1

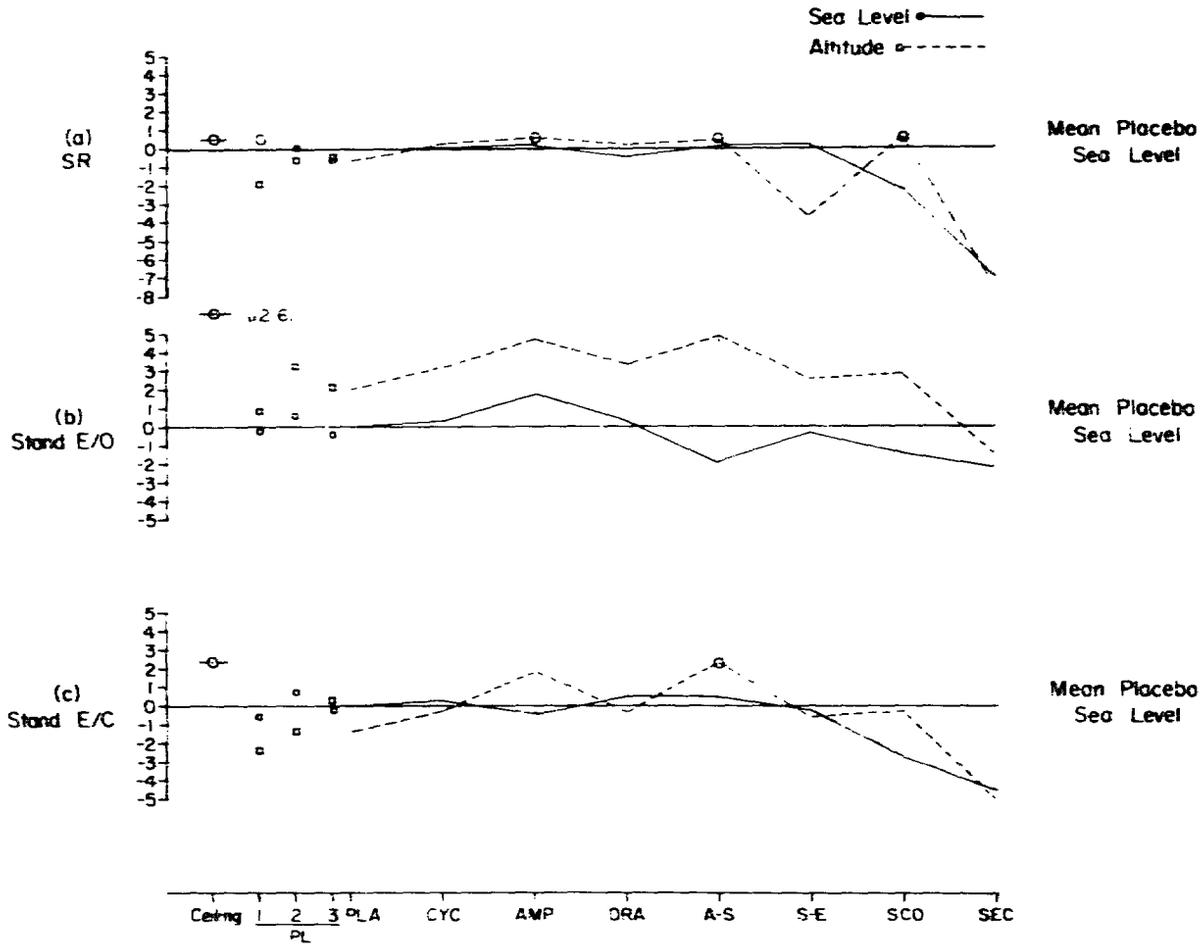

Figure 1

Sea level versus altitude interaction with drugs based on Table III analysis of variance. For purposes of comparison the vertical axis is given in units of standard error. The conversion of ataxia test scores to standard error (SE) units was made using the formula: $Zy = (Y - My \text{ (sea level pla)})/SE$ where SE = square root (Mean Square/9 subjects) shown at bottom of Table III above and below the mean sea leavel placebo (PLA) value on each of the three tests: (a) SR, (b) Stand E/O, (c) Stand E/C. The seven drugs labeled on the horizontal axis are denoted by the symbols given in Table 1. The circled values represent a perfect score by all nine subjects.

In fact, the best Stand E/O performance was at altitude under A-S and the worst was at sea level under A-S and under SEC. Within part (c), Stand E/C, the altitude-level profile may be seen to cross back and forth over the relatively smooth sea-level profile, indicating that performance under different drugs varied at altitude while remaining relatively the same at sea level (except for the drops under SCO and SEC).

A summary of the results of the simple effect of drugs in the set of seven analyses of variance at sea level and three at altitude is given in Table IV. Performance under the different drugs at sea level was significantly different on only four of the ataxia tests: SR ($p < .005$), Stand E/C ($p < .001$), Walk E/O ($p < .01$), and SOLEC-L ($p < .05$); Figure 2 displays these means. At altitude the performance differed significantly on all three of the ataxia tests used: SR ($p < .001$), Stand E/O ($p < .025$), and Stand E/C ($p < .025$); Figure 3 displays these means.

Table IV

Summary of Ten Analyses of Variance--Simple Effect of Drugs at Sea Level and at Altitude

Ataxia Tests	MSe*	SE*	F9,72	p<	MSe	SE	F9.72	p<
SR	875.70	9.8640	3.43	.005	1067.81	10.8924	3.72	.001
Stand E/O	1303.87	12.0363	1.67	.25	1891.47	14.4970	2.60	.025
Stand E/C	524.76	7.6359	3.75	.001	1099.92	11.0545	2.67	.025
Walk E/O	0.54	.2444	2.75	.01				
SOLEC-R	159.34	4.2076	1.21	ns				
SOLEC-L	440.22	6.9938	2.08	.05				
WALEC	31.34	1.8662	0.54	ns				

Statistical analyses of the simple effects of drugs using the Tukey procedure (hsd) of a-posteriori comparisons of all possible pairs of mean differences between secobarbital and the other seven drugs within those ataxia tests having significant F's (four at sea level and three at altitude--Table IV) were made. The results are given in Table V. Secobarbital (SEC) was the only drug found to differ significantly from any other drug; in six cases with A-S; in five with PLA, AMP, and DRA; in four with CYC; in two with S-E; and once with SCO.

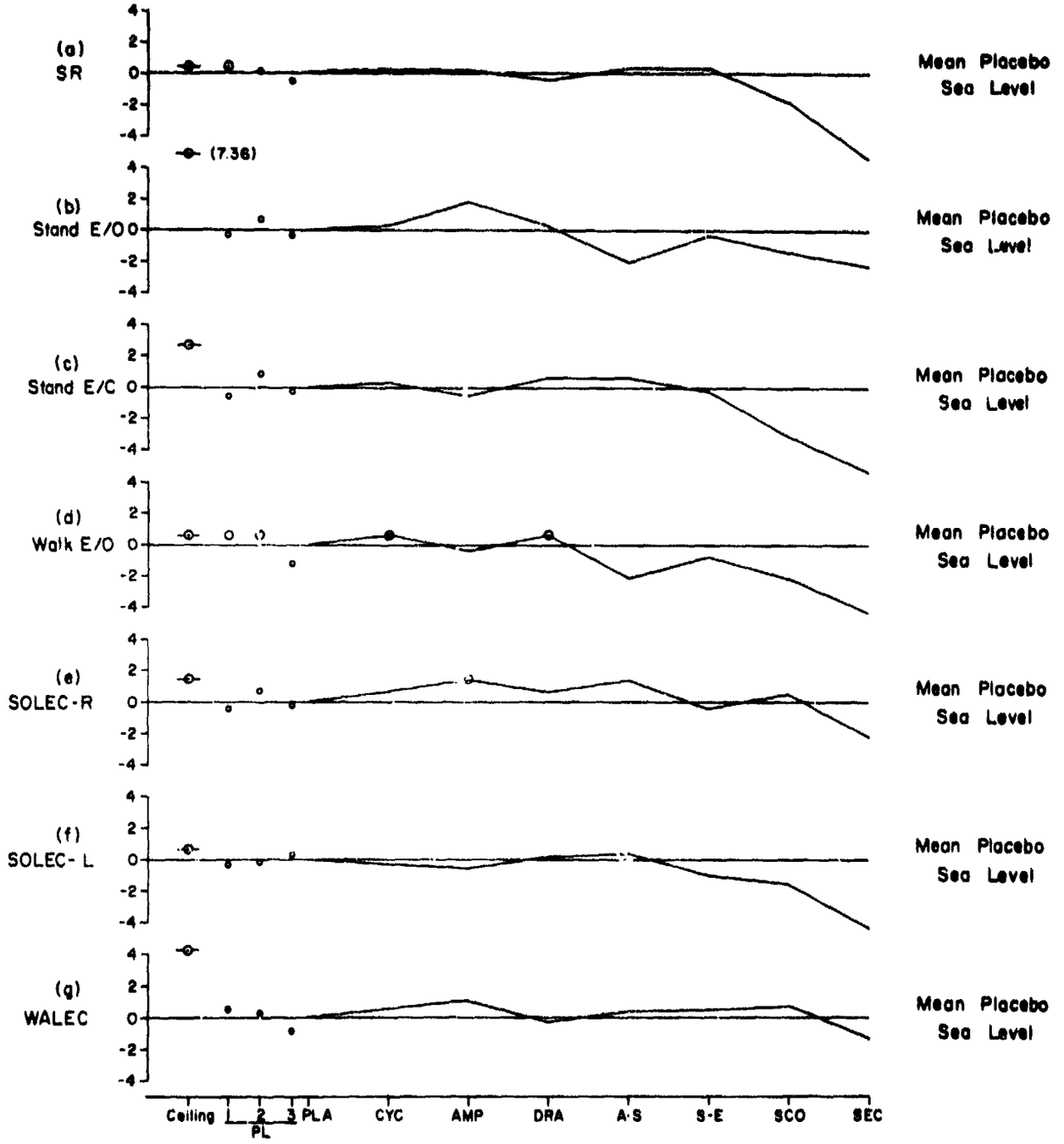

Figure 2

Drug effects at sea level based on Table IV analyses of variance. (See description of Figure 1.) Significant differences given in Table V.

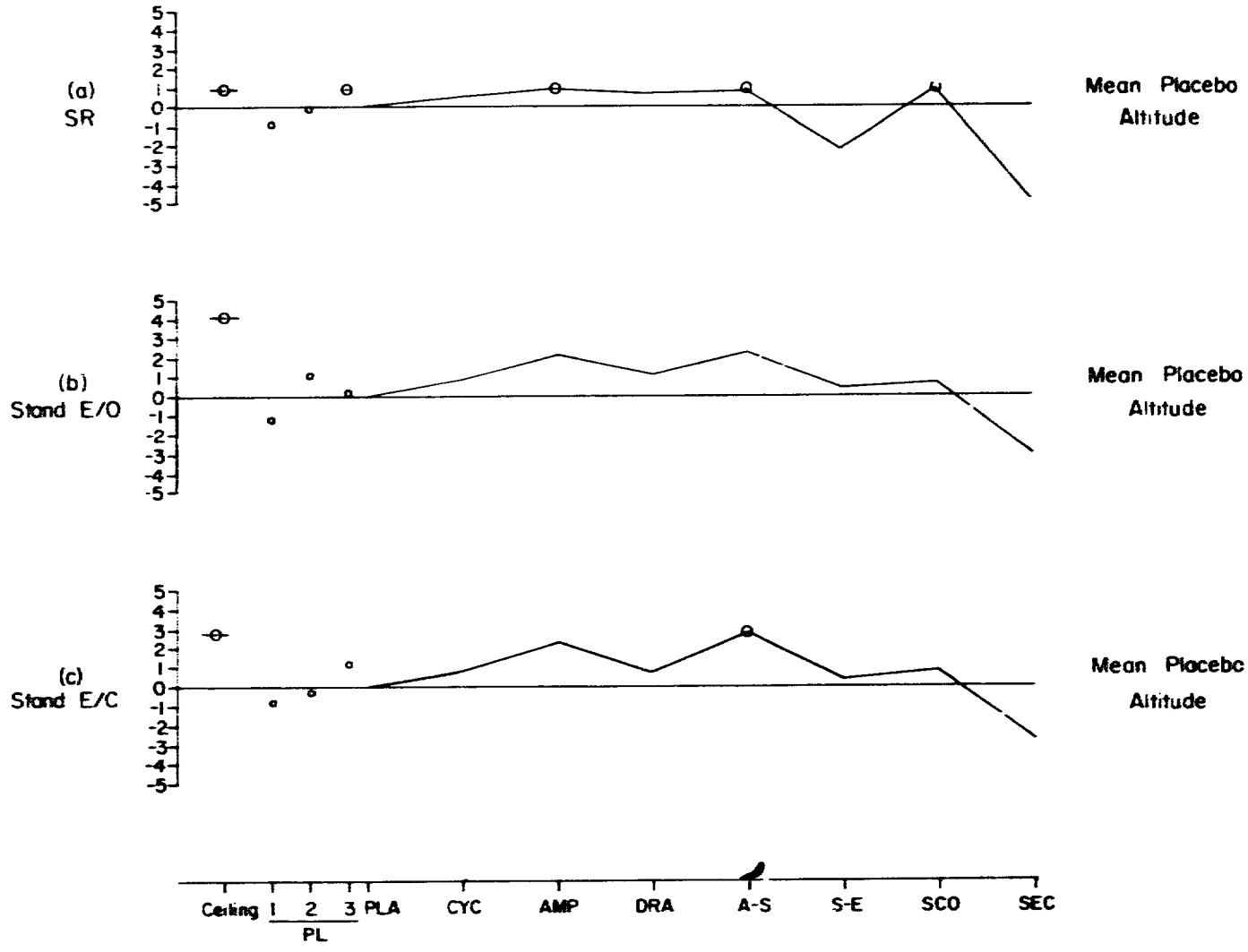

Figure 3

Drug effects at altitude based on Table IV analyses of variance. (See description of Figure 1.) Significant differences given in Table V.

Table V

Significant Differences Between Secobarbital (SEC) and Seven Other Drugs on Postural Equilibrium Functions at Sea Level and at Altitude

	Sea Level (Figure 2)				Altitude (Figure 3)		
Drugs	SR(a)	Stand E/C(c)	Walk E/O(d)	SOLEC-L(f)	SR(a)	Stand E/O(b)	Stand E/C(c)
PLA	**	*	*	*	*	ns	ns
CYC	**	**	*	ns	**	ns	ns
AMP	**	*	ns	ns	**	**	**
DRA	*	**	*	*	**	ns	ns
A-S	**	**	ns	*	**	**	**
S-E	**	*	ns	ns	ns	ns	ns
SCO	ns	ns	ns	ns	**	ns	ns

*p <.05; **p <.01

DISCUSSION

The statistically significant finding that performance on only the Stand E/O test at altitude was enhanced generally, relative to sea level, across drugs is possibly explained by the fact that the other two tests, SR and Stand E/C, had low ceilings (maximum possible scores were often reached) which precluded demonstration of such an effect. For example, on the SR test perfect scores by all nine subjects were attained at altitude under three drugs, thus eliminating any possible higher measurement indicating enhanced performance.

Of special interest, A-S was the only drug that showed a significant difference in its effects between sea level and altitude. This was the depressing effect found at sea level and the enhancing effect found at altitude on Stand E/O test performance which was not found for either d-amphetamine or scopolamine alone nor by any other drug alone or in combination. It is well known that certain drugs have greater effect at altitude than at sea level (7). The unusual nature of our finding, however, requires crossvalidation. If obtained, the implications of this finding, both practical and theoretical, will indeed remain a challenge worthy of further investigation, particularly in view of the greater protection afforded by this drug combination (A-S) in the prevention of motion sickness than by any other drug or drug combination investigated at this laboratory (24). Based on present findings, only, the implication is that, under low-grade

hypoxia conditions, the effect of A-S is stimulatory, or performance enhancing, whereas at sea level it has a depressing and, therefore, an undesirable effect.

The decremental effects of secobarbital on the postural equilibrium functions sampled by the ataxia test battery were highly consistent. There was no significant difference between the effects of this drug shown at sea level compared to 12,000 feet, indicating no significant additive, synergistic, nor antagonistic interaction with the low-grade hypoxia condition. This finding that secobarbital depressed performance is in keeping with the known depressant effects of secobarbital on CNS activity (16,19). For example, the debilitating effects of double the dosage of secobarbital used in this study on complex behavior during a simulated 12-hour flight at sea level has been demonstrated (19). In a study of drug effects in a simulated driving task (16), it was found that secobarbital produced a prompt, intense impairment of performance, which continued throughout the remainder of the day, and produced an impairment of function at least as great as that produced by alcohol when the blood alcohol concentration was 150 mgm percent. Thus the use of secobarbital for the prevention or control of motion sickness seems contraindicated.

The undesirable effects of secobarbital shown in the present study were best demonstrated by the SR and Stand E/C subtests of the ataxia battery at sea level and by the SR test at 12,000 feet; 86 percent of the differences observed between secobarbital effects and placebo effects on each of these tests was statistically significant. At sea level, on the SOLEC-L and Walk E/O subtests 43 percent of the differences between the effects of secobarbital and those of the remaining drugs was statistically significant; however, the Stand E/O, SOLEC-R, and WALEC subtests failed to show any significant differences. On the Stand E/O and Stand E/C subtests, at 12,000 feet, 29 percent of the comparisons between secobarbital and all other drugs was statistically significant. In future studies of drugs, whose effects range from stimulatory to depressant, the use of the three ataxia subtests, SR, Stand E/O, and Stand E/C, would thus appear to have the most value.

Placebo effects at sea and altitude levels did not differ significantly across tests. To the extent that the placebo (drug control) conditions at 12,000 feet simulated altitude were representative of only low-grade hypoxia conditions, no significant effects of hypoxia alone on the performance studied were observed. This result is generally consistent with other studies that evaluated various aspects of psychophysiological performance at altitudes and altitude equivalents in the neighborhood of 12,000 feet (8,12,17,18,20-22). At variance with such general findings is a recent study that revealed a significant increase in reaction time and a significant decrease in movement time from sea level to 7000 feet and 10,000 feet (15).

Comprehensive studies have been addressed to the problem of determining the nature (primarily factorial) of basic human ability tests to evaluate the tests' sensitivity to a variety of drug conditions, and to validate a test battery in terms of its predictability to drug effects in the field (1,5). Crucial to the success of this venture is the development of prototype military criterion tasks, but efforts so far expended have had

only partial success (4,6,13). Applicability of present findings would be limited by the dissimilarity between the drug exposure times investigated and drug exposure times representing widely different operational conditions during which unwanted side effects of motion sickness are (or may be) experienced. Implications of the present study for operational situations as well as for future research are considered to depend in part upon careful evaluation of operationally important behaviors affected during motion sickness.

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